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Via Federal Express

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Proposed Rule on Patent Listing Requirements and Application of 30-Month Stays (Docket No. 02N-0417)

Dear Sir or Madam:

Pfizer Inc submits these comments regarding the Proposed Rule, *Applications for FDA Approval to Market a New Drug: Patent Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not be Infringed*, 67 Fed. Reg. 65448 (October 24, 2002). Although Pfizer supports FDA's efforts to establish clearer regulatory guidance on these issues, Pfizer urges FDA to consider carefully whether its proposals are necessary and proper to achieve the balance of competition and innovation embodied in the "Hatch-Waxman" generic drug law.[1] Pfizer also suggests revisions to certain aspects of the Proposed Rule.

[1] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, 98 Stat. 1585.

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1. Background

The Proposed Rule addresses certain features of the Hatch-Waxman law that are designed to coordinate FDA's generic drug approvals with the outcomes of patent litigation between innovator and generic drug companies. Most significantly, the Proposed Rule would change the operation of the so-called "30-month stay" that prohibits FDA approval of a generic drug application (ANDA) for up to 30 months during the pendency of patent litigation. Relatedly, FDA's proposal would modify patent "listing" procedures that play a critical role in triggering 30-month stays.

As FDA notes in the preamble to the Proposed Rule, the Hatch-Waxman law had the dual objectives of, on the one hand, facilitating drug price competition by expanding opportunities for generic drug entry, and, on the other hand, ensuring proper incentives for the discovery and development of new (innovator) drug products. The 30-month stay plays an important part in this balance by acting as a counterweight to another feature of Hatch-Waxman, known as the *Bolar* amendment, 35 U.S.C. § 271(e)(1), that allows generic manufacturers to infringe on innovator drug patents *before patent expiration* in order to develop generic products.

The head-start that the *Bolar* amendment provides for generic manufacturers—an advantage that is unique in patent law—greatly accelerates generic drug entry. Reciprocally, the head-start also substantially reduces the meaningful life of innovator drug patents. The 30-month stay mitigates some of that patent loss—and some of the windfall to the generic manufacturer—by requiring FDA to withhold approval of the generic drug when the innovator company (whose product the generic manufacturer is copying) initiates litigation to vindicate its patent rights.

The Proposed Rule seeks to revise the 30-month stay in two ways. First, the rule proposes to allow only one 30-month stay for each ANDA. This is a significant change from current law, which allows multiple stays if new relevant patents issue while an ANDA is pending approval. Second, the rule seeks to clarify the types of patents that can trigger a stay, and how those patents get "listed" in FDA's publication *Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book").

The preamble to the Proposed Rule explains that these modifications are motivated by concern that the number of 30-month stays "appears to be increasing over time." 67 Fed. Reg. at 65455. The basis for this concern is a July 2002 report from the Federal Trade Commission, entitled *Generic Drug Entry Prior to Patent Expiration*: An FTC Study (FTC Report). The FTC Report assessed the application of the 30-month stay to generic applications that "challenged" innovator patents between 1992 and 2000 through "paragraph IV certifications" asserting that particular patents were invalid or not infringed. The FTC found that there were 104 innovator drugs subject to such challenges. FTC Report at 10. Out of these 104 drugs, the FTC found only eight in which a generic application was affected by more than one 30-month stay, *id.* at 45; for the 96 other innovator drugs that were subject to patent challenges, at most only one 30-month stay—and in some cases, no stay—applied. The FTC also found that, from 1984 and 2000, only six percent of all generic applications (483 out of 8,019) involved any patent challenges. *Id.* at 10. Taken together, these findings indicate that only a tiny fraction of ANDAs have been subject to even one stay, and an even much smaller percentage (probably well under one percent) have experienced multiple stays.

Notwithstanding that the occurrence of multiple 30-month stays is a demonstrated rarity, the FTC Report suggested that in order to avoid "unwarranted" stays, the law should be revised to allow only one 30-month per ANDA. FTC Report at page v.[2] The Proposed Rule uncritically adopts that suggestion. 67 Fed. Reg. at 65449, 65455.

Pfizer respectfully submits that both the FTC and FDA have overstated the asserted "problem" of 30-month stays, and have rushed to a "solution" that may be broader than warranted by the stay's experience as a feature of the Hatch-Waxman law. Nevertheless, for purposes of this rulemaking proceeding Pfizer reserves judgment on whether, in a broad sense, the regulatory revisions FDA is proposing are necessary or legally appropriate. Pfizer's comments will address some practical implications of FDA's proposal, with the aim of ensuring that the Proposed Rule does not result in unintended consequences that might conflict with the purposes of Hatch-Waxman.

2. Proposed § 314.53 – Patent Listings and Patent Declaration

In the following sections, Pfizer addresses FDA's proposal to revise the regulations in 21 C.F.R. § 314.53 that describe what patents may be listed in the Orange Book, and what information must be provided in the "patent declaration" that is used to submit patents for listing.

a. Patents on Packaging

The Proposed Rule would prohibit the listing in the Orange Book of "patents claiming packaging." This position may be reasonable when, as is often the case, a drug's packaging is "distinct from the approved drug product," and thus not subject to FDA approval. 67 Fed. Reg. at 65451. In some circumstances, however, a drug's

[2] The FTC Report does not support a conclusion that where multiple stays have occurred, they have been "unwarranted."

container or packaging may be integral to the product's use. The Proposed Rule should be modified to accommodate such situations.

For example, novel blister packaging may be necessary to ensure safety or efficacy. Similarly, a drug delivery system—such as an applicator or inhaler, or the constituents of a transdermal patch—may be an integral part of the product. In addition, a drug's packaging or container may be part of a patented method of using a product. Prohibiting all patents on packaging or containers would exclude relevant patents covering these mechanisms.

Pfizer thus proposes that FDA revise the Proposed Rule to allow listings of patents that claim packaging, containers, or delivery systems, if FDA would require prior approval for any changes in those elements. FDA should only exclude such patents where it is clear that FDA would permit a change in the packaging or container without prior approval.

b. Product-by-Process Patents

Pfizer supports FDA's proposal to require listing of product-by-process patents. As the preamble to the Proposed Rule notes, a product-by-process patent claim defines a drug product at least in part in terms of the method or process by which the product is made. Although such claims may be limited by the recited process steps, product-by-process claims are only infringed by the product itself. *See Atlantic Thermoplastics Co., Inc. v. Faytex Corp.*, 970 F.2d 834 (Fed. Cir. 1992). Moreover, the patentability of a product-by-process claim is dependent on the novelty and non-obviousness of the product in terms of its structure, independent of its method of manufacture or recited process steps. *See In re Thorpe,* 777 F.2d 695 (Fed. Cir. 1985); *see also Manual of Patent Examining Procedure* § 2113 (8th ed. 2001). Because a product-by-process patent claims

a drug substance or product and could support a reasonable allegation of patent infringement against a generic applicant, it meets the criteria for patent listing in 21 U.S.C. § 355(b)(1).

The concern expressed in the Proposed Rule about the difficulty of distinguishing product-by-process patents from process patents could be addressed by adding the following italicized language to proposed section 314.53(b):

> For purposes of this part, such patents consist of patents that claim the drug substance (ingredient), patents that claim the drug product (formulation and composition), *patents that claim the drug substance or drug product at least in part in terms of its method of manufacture (product-by-process patents),* and patents that claim a method of use.

c. Patents on Methods of Use

Noting that the Proposed Rule would prohibit the listing of patents claiming uses "that are not approved for the listed drug or are not the subject of a pending application," FDA contends that this is a continuation of current law. 67 Fed. Reg. at 65452. In fact, however, the Hatch-Waxman statutory listing provision allows the listing of patents claiming unapproved uses in some circumstances. Moreover, the patent declaration in the current version of section 314.53, which tracks the words of the statute, also accommodates such listings. FDA should revise the Proposed Rule so that it is consistent with the governing statute.

The statutory listing provision, 21 U.S.C. § 355(b)(1), requires an NDA applicant to list a patent if (1) the patent "claims a method of using" the NDA drug, and (2) "a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." These statutory criteria are satisfied when, as is the theory of several ongoing pharmaceutical patent infringement cases, the marketing of a generic drug with approved labeling for one use induces

infringement of a patent for an unapproved use. The listing requirement is not limited to patents claiming approved uses.[3] *See Purepac Pharm. Co. v. Thompson*, No. 02-1657, slip op. at 7-8 (D.D.C. Dec. 16, 2002) (noting that FDA's policies prohibiting listing of patents claiming unapproved uses "are not statutory requirements, but rather have been imposed by regulation").

By providing for the listing of patents claiming unapproved uses, the statute ensures that generic manufacturers are forewarned of circumstances in which the marketing of a generic drug could lead to charges of patent infringement. Although the Proposed Rule recognizes and seeks to preserve this benefit in another context, FDA's proposal to prohibit the listing of patents claiming unapproved uses works against it: in the agency's own words, the proposal "could mislead potential ANDA applicants into submitting ANDAs . . . infringing the patent . . . [FDA] in turn, could expend resources on reviewing an ANDA for a drug that is covered by the unlisted patent, and the patent owner could expend resources in defending the patent." 67 Fed. Reg. at 65453. The inconsistency between FDA's regulatory position and the language and purpose of the statute also may create other difficulties in the implementation of Hatch-Waxman, as illustrated by the recent litigation in *Purepac*.[4]

FDA's regulatory restriction against the listing of patents claiming unapproved uses also is inconsistent with the agency's oft-repeated acknowledgement that it lacks

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[3] This appeared to be FDA's interpretation of the statute shortly after Hatch-Waxman's enactment. In an October 31, 1986, letter to "All NDA and ANDA Holders and Applicants," FDA asked NDA applicants to "state which indications or other conditions of use covered by a patent are approved [for inclusion in labeling]."

[4] In *Purepac*, FDA's incorrect regulatory position on use patents led the agency to misunderstand a patent listing and as a result to take inappropriate action on a pending ANDA. *See Purepac*, slip op. at 14, 27-31.

expertise in patent matters. Although litigation on the issue is ongoing, at least some courts have held that a patentee who asserts the inducement theory described above has made a proper a claim of patent infringement. *See, e.g., Warner-Lambert co. v. Apotex Corp.*, 1999 WL 259946 (N.D. Ill. Apr. 8, 1999), *appeal pending*. Thus, it is inappropriate for FDA, by prohibiting listing of patents claiming unapproved uses, to take the position that no such claim of infringement "could reasonably be asserted."

Accordingly, FDA should revise proposed section 314.53(b) so that it permits patent listings in situations in which the marketing of a generic drug for an approved use could infringe, by inducement, a patent covering an unapproved use. FDA should also revise the patent declaration in proposed section 314.53(c)(2)(E), and related language in proposed sections 314.52(a)(3) and 314.95(a)(3), so that they are consistent with the statute in this regard.

d. Patents on Alternative Forms of a Drug Substance

The Proposed Rule requires the listing of patents that claim alternative forms of a drug substance that are "the same as" the approved drug. Pfizer agrees that such patents should be listed. As FDA notes in the preamble, allowing listing of alternative drug forms is appropriate because FDA generally presumes that alternative forms are "the same as" the listed drug, and thus approvable through an ANDA.

Pfizer disagrees, however, with how FDA proposes to implement this listing requirement. The Proposed Rule would require that, in order to list a patent claiming an alternative drug form, the NDA holder would have to assert in a signed declaration that the alternative form is "the same as" the approved drug and thus subject to approval through an ANDA. Proposed § 314.53(c)(2)(C)(3). Pfizer respectfully submits that it is

inappropriate for FDA to place the burden on the NDA holder of making the scientific determination of "sameness."

As FDA observes in the preamble, "Whether two different drug substances are the 'same' active ingredient is a scientific determination based upon the specific characteristics of the drug substances involved." 67 Fed. Reg. at 65452. Thus, the precise parameters of "sameness" may vary with the characteristics of a generic product. When the NDA holder files its patent information, however, it has no information about what alternative forms ANDA applicants might seek to have approved, and knows nothing about the particular characteristics of potential generic products.[5] Thus, the NDA holder is in no position to make an assessment of "sameness." For this reason, it is unreasonable to shift the statutory burden of showing "sameness" from the ANDA applicant to the NDA holder, as FDA's proposed patent declaration seeks to do.

Pfizer proposes that FDA revise the Proposed Rule (including the requirements of the patent declaration) to allow an NDA holder to list a patent claiming an alternative drug that *could* be considered "the same as" the approved drug. This ensures that generic applicants are on notice of the full extent of the patent rights relating to the drug substance. It also avoids the prejudice and burden on NDA holders that flows from requiring a definitive acknowledgement of "sameness."

3. Proposed Limitation on 30-Month Stay

As the Proposed Rule acknowledges, the Hatch-Waxman law plainly authorizes additional 30-month stays each time an ANDA is amended to include a new paragraph IV certification, and FDA consistently has applied the stay in this manner since Hatch-

[5] This problem is exacerbated by the fact that many drug substance patents claim a variety of possible alternative forms.

Waxman's enactment in 1984. The Proposed Rule seeks to radically revise FDA's regulatory approach by allowing only one 30-month stay per ANDA. As noted earlier in these comments, in light of Hatch-Waxman's purposes and the experience of its implementation, it is highly dubious that such a limitation is necessary or appropriate. However, assuming *arguendo* that the result FDA seeks—one 30-month stay per ANDA—is justifiable, several changes to the Proposed Rule would be required if that result is to be achieved without compromising other important interests.

One obvious and significant problem with FDA's proposal is that it creates an opportunity for an ANDA applicant to avoid *any* 30-month stay. When (as is often the case) there are multiple patents listed for a drug, the ANDA applicant could file a paragraph IV certification against a narrow patent that is easily designed around, such as a formulation patent, and make paragraph III certifications regarding other listed patents that are more likely to be infringed. If the NDA holder is unable to sue for infringement of the narrow formulation patent, there would be no 30-month stay. At that point, the ANDA applicant could amend its ANDA by changing the initial paragraph III certifications to Paragraph IV certifications. Under the Proposed Rule, no paragraph IV notice would be required and no opportunity for a 30-month period would be available for those new certifications. The regulatory revisions proposed by PhRMA should help correct this problem.

Another serious flaw in the Proposed Rule is that, by eliminating the ANDA applicant's obligation to notify an NDA holder of new paragraph IV certifications, it may delay the initiation of patent litigation until after a generic drug enters the market. This result directly undermines the design of Hatch-Waxman. By deeming the filing of an

ANDA to be an act of patent infringement, 35 U.S.C. § 271(e)(2), Hatch-Waxman allows patent litigation to commence (and in some cases to be resolved) during the FDA review period before a generic drug is marketed. This benefits all parties (the NDA holder, the ANDA applicant, and the public), because early resolution of patent issues helps avoid market disruptions and confusion that could result from patent judgments that issue after a generic product has launched. Under FDA's proposal, however, patent litigation would be delayed because the NDA holder, having received no paragraph IV notice, would not become aware that a patent is being challenged until FDA approves the ANDA.

One way to correct this would be for FDA itself to notify the NDA holder about a patent challenge in an ANDA. To make this work, the Proposed Rule should provide as follows: When an ANDA applicant submits to FDA a second (or subsequent) paragraph IV certification, the applicant must also file with the agency "a detailed statement of the factual and legal basis" for challenging the NDA holder's patent—in sum, the same information that would be required in a paragraph IV notice under 21 U.S.C. § 355(j)(2)(B)(ii). FDA would then forward this information to the NDA holder. This procedure would avoid the direct notice from the ANDA applicant to the NDA holder that could trigger a new stay, but it would ensure that patent litigation could be commenced at the earliest opportunity available under the statute.

As these problems with the Proposed Rule illustrate, the radical revision of the 30-month stay that FDA seeks to effect is difficult to reconcile with the design and policies of Hatch-Waxman, and is liable to create numerous unintended consequences. Pfizer has pointed out some readily apparent difficulties with FDA's proposal, but there

are likely to be others. FDA thus should proceed cautiously in implementing regulatory revisions in this area of the law.

4. Conclusion

As explained above, several of FDA's proposals require further consideration and significant revision. Because of the complexity of the underlying statute, and the importance of the interests it serves, Pfizer recommends that FDA re-publish the Proposed Rule for further comment before finalizing it.

Respectfully submitted,

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